REMARKS/ARGUMENTS

Claims 1, 2, 6-8 and 11-17 are currently pending in the above-identified application. Claims 1, 6, and 11-15 have been amended as set forth in detail below. Support for these amendments is identified in the following remarks. No new matter is added by these amendments.

Rejections under 35 U.S.C. §112:

Claims 1, 2, 6-8 and 11-17 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner states that "a generic statement such as 'T cell co-stimulatory molecule' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by the property of being able to bind to a T cell ligand and provide a second signal for optimal stimulation of the primary antigen specific signal." On this basis, the Examiner believes the claims to contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

While not agreeing with the Examiner's rejections nor reasons for rejection, but to further expedite prosecution of the instant application, Applicants have amended claims 1, 6, and 13-15 to recite a "B7 co-stimulatory molecule." Support for this amendment can be found in the specification at, for example, page 5, lines 7-9, and page 38, line 9. Further, claim 11 has been amended for consistency with amended claim 1 upon which it is dependent.

It is noted that, as used in the present application, "B7" refers to a family of surface receptors, well-known in the art at the time of filing the instant application, having particular structural and functional characteristics, including binding with CD28 and CTLA-4 on T cells. At the time of the present invention, the amino acid sequence of a number of "B7 co-stimulatory molecules" were known and are described in the specification as filed (*see* page 27, lines 19-30, incorporating various publications by reference), and regions of homology between these members had been designated (*see, e.g.*, U.S. Patent No. 5,942,607.)

In light of the above, it is respectfully submitted that the skilled artisan reading the specification as filed would accept that Applicants were in possession of the methods as presently recited in claims 1, 2, 6-8 and 11-17. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the above rejections of claims 1, 2, 6-8 and 11-17 as lacking written description under 35 U.S.C. § 112, first paragraph.

Claims 1, 2, 6-8 and 11-17 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the invention. The Examiner believes that the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims "encompass a method of administering a nucleic acid molecule non-viral vector comprising a polynucleotide encoding a T cell co-stimulatory molecule and further comprising any peptide or protein antigen, including those from HIV, *i.e.*, a method for vaccination against HIV" (emphasis added).

First, the Examiner contends that there is insufficient guidance in the specification as to how to make and/or use the non-viral vector comprising a polynucleotide encoding a T cell co-stimulatory molecule. While not agreeing with the Examiner, Applicants believe this aspect of the rejection to be obviated by the amendments to claims 1, 6, and 11-15, as set forth above, to recite "B7 co-stimulatory molecule." As previously noted, the B7 family of co-stimulatory molecules was well-known in the art as of the effective filing date of the instant application. Further, the B7 family, including amino acid and nucleotide sequences for B7-1, B7-2, B7-3, and B7H, are described in the specification at, *e.g.*, page 27, lines 24-28 (incorporating various publications by reference, *see supra*).

Second, Applicants wish to note that claims 1, 2, 6-8 and 11-17 are not directed to any peptide or protein antigen, but to only those peptides and/or protein antigens that comprise one or more T cell epitope(s). Further, Applicants believe the Examiner's reliance on Letvin (*J. Clin. Investigation* 109:15-20, 2002) and PROMT Accession No. 1998: 555242 (hereinafter Reference 555242) to be misplaced. The Examiner apparently believes these references, which

review the status of development of HIV protective vaccines, to support the contention that the specification is not enabling with respect to eliciting an immune response to "any peptide or protein antigen." For the reasons set forth below, Applicants submit that Letvin and Reference 555242 are insufficient to rebut Applicants' presumption of an enabling disclosure for the methods as claimed.

First, the Examiner does not argue, nor do Applicants believe that it can be credibly asserted, that the specification does not teach the steps of administering (1) an immunogenically effective amount of a peptide or protein antigen comprising one or more T cell epitopes coordinately with (2) a non-viral vector comprising a polynucleotide encoding a B7 co-stimulatory molecule. The Examiner also does not argue that it is infeasible or even difficult to practice these steps, in view of the teachings of the specification and the knowledge of the skilled artisan at the time of the invention. Instead, the Examiner apparently believes that a person of ordinary skill who performs these steps will not obtain the desired elicitation of a protective immune response to any antigen, including those recited in the instant claims comprising one or more T cell epitope(s), including those from HIV proteins. Thus, it is submitted that the true thrust of this aspect of the rejection is an alleged lack of utility (and, therefore, an alleged lack of "how to use" the invention under 35 U.S.C. § 112, first paragraph).

As the Examiner is aware, the standard of review for compliance with both § 101 and § 112, first paragraph, regarding the "credibility" of an asserted utility, are set forth in MPEP §§ 2107.01-2107.03. The claimed invention is the focus of the utility inquiry, and an applicant need only make one credible assertion of utility to establish utility of the invention as a whole. MPEP § 2107.02(I). A *prima facie* showing of no utility must establish that it is more likely than not that a person skilled in the art would not consider the statement of utility credible. *See id.* at (III)(A). Further, the Examiner must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that show that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. *See id.* Moreover, the MPEP states that "Office personnel should also be especially careful not to read into a claim unclaimed results, limitations, or embodiments of an invention,"

as doing so can "inappropriately change the relationship of an asserted utility to the claimed invention and raise issues not relevant to examination of that claim." *Id.* at (I).

With respect to the standards set forth above, it is noted that at least one asserted utility for the present invention is the supplementation and enhancement of a peptide-based immunogen wherein that peptide comprises one or more T cell epitope(s). (*See, e.g.*, specification at page 5, lines 14-18, and page 6, lines 1-3.) It is respectfully submitted that the skilled artisan reading the specification would understand that supplementation and enhancement of a peptide-based immunogen simply requires an increased immune response to the peptide antigen using the claimed methods (including co-administration of a non-viral vector encoding a B7 co-stimulatory molecule), relative to an immune response elicited in the absence of these methods.

In view of the above, Applicants note the following with regard to the Examiner's citations to Letvin and Reference 555242.

Letvin

First, the Examiner cites to Letvin as stating that the "universal persistence of viral replication in spite of potent immune responses raises the specter that no vaccine-elicited immune response may be capable of fully eliminating or containing indefinitely the replication of HIV" (page 15, right column, second paragraph (emphasis added)). However, Applicants note that a particular result is not recited in the body of any of the rejected claims. Because the claims do not recite any limitation requiring the full elimination or indefinite containment of a viral pathogen, Applicants believe this statement to be irrelevant to the present claims. *See* MPEP § 2107.02(I), *supra*. As indicated above, Applicants have asserted that the present invention is useful for enhancing or supplementing a peptide-based immunogen. It is submitted that the skilled artisan reading the specification as filed would reasonably accept that coordinate administration of a non-viral vector encoding B7 with a protein or peptide antigen comprising one or more T cell epitope(s) from a virus, such as for example HIV, would enhance the immune response to that antigen, and that such enhancement of the immune response against the virus

would be useful for, for example, killing the virus (including HIV) in a immunized individual, whether or not full elimination or indefinite containment of the virus (HIV) is achieved. It should be noted that many of the compositions that have been approved by the Federal Drug Administration for the treatment of HIV, including for example many of the nucleoside analogs and protease inhibitors currently sold commercially, fail to "fully eliminate" or to "indefinitely contain" HIV. It appears that the Examiner may be establishing a threshold for utility and/or written description that is unreasonable and not pertinent to the present invention as claimed.

Second, the Examiner states that Letvin teaches the absence of CTL responses to HIV subunit vaccines in clinical trials (*see* Table 1). It should be noted that the subunit vaccines discussed by Letvin are soluble recombinant proteins which are processed in the MHC class II pathway which elicits helper T cells and antibodies, and therefore would not be expected to elicit a CTL response. However, the claims do not require a CTL response, nor are the claims directed at preventing HIV infection as the review notes at page 16, right column, line 23-25. As set forth in the specification, the disclosed methods may include coordinate administration of a peptide or protein antigen comprising T helper or B cell epitopes as well. (*See* specification at page 64, lines 1-5.) Letvin teaches that HIV subunit vaccines elicited modest antibody responses which does not suggest that the claimed methods would not be useful for enhancing this humoral immune response by, *e.g.*, further eliciting T cell help.

The Examiner also cites to Letvin for the proposition that an HIV vaccine "will require more than a single vaccine modality." In view of the reference as a whole, Applicants interpret this statement as referring to an HIV vaccine that is capable of fully eliminating and containing indefinitely the replication of HIV. As discussed above, full elimination or indefinite containment of a viral pathogen is irrelevant to enablement of the present claims in view of the asserted utility of the claimed methods for enhancing or supplementing peptide-based vaccines. Further, it is respectfully submitted that the present invention would be equally applicable to development of vaccines having more than a single modality, since the methods can be used in conjunction with an antigen(s) having, *e.g.*, both a neutralizing antibody epitope, a helper T cell epitope and/or a CTL epitope.

The Examiner also relies on Letvin as teaching that viral mutations allow escape from CTL recognition. However, in the cited studies, "impressive early CTL control of replicating virus and clinical protection" were observed prior to "escape from CTL recognition" due to accumulated virus mutations. It is respectfully submitted that the skilled artisan would reasonably accept the claimed methods would be useful for enhancing and supplementing this initial CTL control of replicating virus. Such enhancement would contribute to the restriction of viral replication to lower levels, which, according to Letvin, would cause viral mutations to occur less frequently. (*See* Letvin at page 19, column 2, last paragraph.) Further, for the reasons set forth above, the Examiner has not shown such enhancement and supplementation of a peptide-based vaccine would not be credible. Accordingly, Applicants believe that escape of HIV from CTL recognition due to viral mutations to be insufficient to establish non-enablement of the present invention.

Reference 555242

The Examiner cites to Reference 555242 as stating that virus variability is an important problem facing HIV vaccine researchers, that researchers have very little idea about what constitutes protective immunity or which animal model is best suited to test vaccine candidates, and that the gap between a vaccine candidate and product development remains vast and ethical concerns surrounding clinical trials have yet to be resolved.

Applicants again respectfully remind the Examiner that unclaimed results, limitations, or embodiments of an invention should not be read into a claim during examination, as doing so can "inappropriately change the relationship of an asserted utility to the claimed invention and raise issues not relevant to examination of that claim." MPEP § 2107.02(I). As set forth in detail above, the pending claims do not claim indefinite protection as a particular result. Further, the specification asserts, *inter alia*, that the methods are useful for enhancing and supplementing peptide- and protein-based immunogenic compositions. Therefore, Applicants reiterate that the only issue with respect as to whether the specification teaches "how to use" the

claimed methods is whether Reference 555242 provides sufficient reason to doubt this asserted utility.

In this regard, Applicants note that virus variability, *a priori*, does not preclude enhancement of an immune response to any particular peptide- or protein-based immunogenic composition using the claimed methods.

Further, the claims do not require elicitation of a protective immune response. Because the remaining statements in the reference (regarding product development, use of animal models for testing candidates, and ethical concerns surrounding clinical trials) are also directed to issues relating to achievement of a protective immune response, Applicants believe these statements to be irrelevant as well. Moreover, with regard to inventions having pharmacologic utility, the Federal Circuit has stated that "[t]he stage at which an invention ... becomes useful is well before it is ready to be administered to humans. Were we to require [clinical testing in humans] in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas ...." *In re Brana*, 34 USPQ2d 1436, 1442-43 (Fed. Cir. 1995).

For the reasons and amendments set forth above, Applicants believe claims 1, 2, 6-8 and 11-17 to be enabled by the specification as filed. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 6-8 and 11-17 as non-enabled under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. §103(a)

Claims 1, 2, 6-8 and 11-17 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 5,738,852 (of record) in view of WO 98/04705 (document and CAPLUS Accession No. 1998: 106018 summary of document, of record) and Kaufmann *et al.* (*Cell. Immunol.* 1996, 169/2 246-251, of record) and further in view of statements in the specification on page 37 at lines 7-18. The Examiner believes that it would have been *prima*

facie obvious to one of ordinary skill in the art at the time the invention was made to have administered the viral polypeptide(s), including the HP7 polypeptide, and a co-stimulatory molecule, such as B7.1, as a combination of a polypeptide antigen and a polynucleotide encoding the co-stimulatory molecule or vice versa. The Examiner contends that one of ordinary skill in the art would have been motivated to do this because "U.S. Patent No. 5,738,852 discloses that the vaccines can be administered as polynucleotides and WO 98/04705 and the CAPLUS Accession No. 1998: 106018 teach that the vaccines can be [administered] as either polynucleotides or as peptides to achieve the common function of eliciting immunity to the viral polypeptide(s)," and "the specification teaches the direct injection of naked DNA expression vectors into vertebrate tissues has been shown to result in the uptake of DNA and long term expression of the protein encoded by the DNA."

The Examiner includes claim 15 in the above rejection, stating that it would have been *prima facie* obvious to have administered the antigen and polynucleotide "to proximal target sites selected from the same, or closely adjacent ... sites," and that "'closely adjacent' can be broadly interpreted to read on sites of undetermined distance."

Applicants must again respectfully traverse the instant rejection. As stated previously, in order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must show a motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. MPEP § 2143. Applicants believe that the Examiner has not established a motivation or suggestion to combine the cited references in the manner posited in her remarks. The Examiner appears to believe that the motivation to combine the references arises from alleged art-recognized suitability of the recited compositions for an intended purpose. In this regard, and in view of the Examiner's statement that a motivation to combine arises from an "expectation that the prior art elements will perform their expected functions ...," Applicants interpret the apparent basis for the rejection as the existence in the art of an alleged "expectation" that a non-viral vector encoding a full length co-stimulatory molecule, when coordinately administered to an individual with a peptide or protein antigen, would elicit an enhanced antigen-

specific immune response. However, the cited references cited do not reasonably convey to the skilled artisan the suitability of co-administration of a non-viral vector for *in vivo* transgene expression of a full length co-stimulatory molecule to enhance antigen-specific immune response, particularly where the antigen is administered in a different form and at a different site and time from that of the B-7 co-stimulatory molecule (*i.e.*, as a peptide or polypeptide rather than as a vector encoding a full length B-7 co-stimulatory molecule). There is no disclosure or suggestion in the references, for example, that *in vivo* administration of a peptide or protein antigen with co-administration at a proximal site of a vector encoding a B-7 co-stimulatory molecule will result in expression of a functional full length B-7 co-stimulatory protein; nor that the B-7 co-stimulatory molecule will be coordinately expressed or concurrently present with the peptide or polypeptide antigen so as to increase the immunological function of lymphocytes responding to antigen co-administered of the polypeptide, as is shown in the instant specification. Neither US 5,738,852 nor WO 98/04705 demonstrate *in vivo* co-stimulatory function of B7.1 expressed from naked DNA, but rather disclose the administration of an antigen and a co-stimulatory molecule in the same form. For example, US 5,738,852 states "APCs which express a target antigen and are capable of stimulating a T cell response, preferably a CTL response, are created with in vivo or in vitro by the insertion of one or more recombinant polynucleotides containing a sequence encoding at least one costimulatory molecule and at least one target antigen polypeptide". See column 8, lines 41 - 47. Further, WO 98/04705 and the abstract of the application which appears as CAPLUS Accession No. 1998:106018 disclose the combination of an early and late polypeptide, and optionally a co-stimulatory molecule wherein the polypeptides and the co-stimulatory molecule are provided either as polypeptides or polynucleotides encoding the polypeptides. The polypeptides are provided in a single composition. There is no suggestion or disclosure of providing the antigen as a polypeptide form and the administration of the co-stimulatory molecule as a polynucleotide in a separate composition at a proximal site and even at a subsequent time. Furthermore, Kaufmann *et al.* relates to transfection of cervical cancer cell lines *in vitro* with a gene encoding B7.1 and their use as antigen presenting cells in an *in vitro* cytotoxicity assay. Thus, the references themselves do not reasonably evince an expectation in the art that a polypeptide or protein antigen

administered proximally to a polynucleotide encoding a co-stimulatory molecule, as recited in the instant claims, will have the necessary *in vivo* co-stimulatory activity; nor has the Examiner cited other art evincing such an expectation.

For the reasons set forth above, Applicants believe that claims 1, 2, 6-8, and 11-17 are non-obvious and that the Examiner has not set forth sufficient evidence demonstrating a motivation to combine the cited references in the manner posited. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 2, 6-8, and 11-17 under 35 U.S.C. § 103(a).

Claims 1, 2, 6, and 11-17 are further rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,245,525 (hereinafter "Martelange") in view of statements in the specification on page 37 at lines 7-18. The Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art to "have administered the peptide or protein antigen disclosed by [Martelange] coordinately with ... naked DNA encoding B7 disclosed by [Martelange], and as taught by ... prior art admissions in the instant specification for injection and subsequent long-term expression of the protein encoded by DNA when injected as naked DNA."

Claims 7 and 8 also stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Martenlange in view of statements in the specification at page 37, lines 7-18, as applied to claim 1, 2, 6, and 11-17, and in further view of WO 98/04705 (and the CAPLUS Accession No. 1998: 106018 summary to the document) and Kaufmann et al. (above).

Applicants respectfully traverse the above rejection. Martenlange teach at column 32, lines 39-50 that "[o]ther delivery mechanisms for the B7 molecule would include nucleic acid (naked DNA) immunization (reference omitted) and recombinant viruses such as adeno and pox (reference omitted). These systems are all amenable to the construction and use of expression cassettes for the co-expression of B7 with other molecules of choice such as the antigens of fragment(s) of antigens discussed herein" (emphasis added). Therefore, Martenlange teach or suggest that the naked DNA construct should express both the B7 antigen and the

peptide or polypeptide antigen. This is not an element of the present claims. This teaching is also does not lend itself to peptides that are different from an expression vector or plasmid. Peptides would ordinarily have to be taken up by dendritic cells and carried to a draining lymph node where they would be presented to T cells. It would not have been obvious prior to the present invention that injecting a DNA plasmid expressing a B7 costimulatory molecule at an adjacent site or at a different time would do anything to improve the presentation of the peptide.

In regard to claims 7 and 8, Martenlange discloses as discussed above the co-expression of B7 and an antigen of interest as naked DNA or a virus expression vector and not the administration of an immunologically effective amount of a peptide or protein antigen comprising one or more T cell epitope(s) coordinately with a non-viral vector comprising a polynucleotide encoding a B7 co-stimulatory molecule. WO 98/04705 and Kaufmann et al. have also been discussed above and contrary to the assertions of the Examiner do not provide sufficient evidence of reasoning why the skilled artisan at the time of the present invention would have substituted an HPV protein or peptide antigen as claimed because of, for example, the difference in processing of the peptide or protein antigen and the non-viral vector encoding the B7 co-stimulatory molecule by the immunized individual as set forth above.

In view of the remarks set forth above, Applicants believe claims 1, 2, 6-8, and 11-17 to be nonobvious over the cited art. Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1, 2, 6-8, and 11-17 under 35 U.S.C. § 103(a).

References cited in IDS

In response to the Examiner's request, Applicants are enclosing a complete set of the references as filed with the Form 1449 on February 3, 2003.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 6 August 2004 By: Brian W. Poor

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